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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,134	07/02/2002	Raghuveer Basude	46528-5059-00-US	8214

7590 08/20/2008

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EXAMINER	
EBRAHIM, NABILA G	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
08/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,134	BASUDE ET AL.	
	Examiner	Art Unit	
	NABILA G. EBRAHIM	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Applicant's remarks and amendments to the claims dated 9/5/07 is acknowledged.

Status of Claims

Claims 1-17 are pending in the application.

Claim 17 is new.

Status of Office Action: Non-Final.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite "A surface stabilized microbubble formed without surfactant, said microbubble consisting essentially of (a) a microparticle, wherein said microparticle does not comprise a surfactant, said microparticle having a hydrophobic surface or an affinity for a specific gas, wherein the microbubble is formed without a surfactant and (b) a gas microbubble, wherein said microbubble does not comprise a surfactant". The specification does not include specifically described exclusion of a surfactant. Note that the mere absence of a positive recitation is not basis for an exclusion. The mere absence of a positive recitation in the specification is not basis for an exclusion. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). **This is a new matter rejection.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a microbubble, wherein the microbubble does not comprise a surfactant, then claims 15 and 16 recites that the microbubble of claim 1 is made from at least one of compounds that are surfactants or encompass surfactants such as polyvinyl alcohol, and cellulose and the coating recited in claim 16 also encompasses surfactants. The claims are ambiguous as they do not clearly show what is included or excluded.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasor 5141738 or Schneider US 5271928 in view of Unger US 5542935 (hereinafter "Unger") and further in view of Hugh D. Van Liew et al. Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization Journal of Applied Physiology Vol. 82, No. 6, pp. 2045-2053, June 1997 (Hugh).

Rasor discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (col. 8, lines 24-26) and a gas microbubble, (col. 6, lines 3-11). The gas microbubble attaches or in contact with the microparticle, (column 6, line 57). The compositions are prepared by methods including storing the microparticle in a gaseous environment and

introducing the microparticles into a liquid, (col. 9 bridging to 10 and examples). Also, since the microparticle contains a lipophilic surface, it would have affinity for lipophilic gases such as perfluorocarbons that are somewhat lipophilic by nature. In addition, the step of forming the gas microbubble recited in claim 1 and 2 of the current application is considered a product by process limitation, wherein only a specific single step excludes adding surfactant, this limitation does not exclude surfactant in the microbubble and consequently does not differentiate over the prior art. Rasor also teaches that the ultrasonic diagnostics comprising a liquid vehicle containing (a) suspended therein microparticles of a mixture of at least one C_8 -C_{20} fatty acid and at least one solid that is not a surfactant and (b) microbubbles (abstract), the disclosure does not include the surfactant and is administered intravenously (into the blood).

Schneider discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (such as, a liposome) and microbubbles, which are associated therewith, in that the liposomes stabilize the microbubbles, see (col. 4, lines 6-36). The compositions are prepared by a method of storing the liposomes in a gaseous environment and introducing the liposomes into a liquid, (col. 4, lines 37-55). The compositions may further include drugs, such as radionuclide for nuclear medicine, (col. 10, lines 3-5) as well as, a targeting moiety, (column 9, lines 36-66). Also, since the microparticle contains a lipophilic surface, it would have affinity for lipophilic gases such as perfluorocafbons that are somewhat lipophilic by nature. Schneider also disclosed that his composition is suitable for injection into the bloodstream and body cavities of living beings, comprising a suspension of stabilized air or gas microbubbles in a physiologically acceptable aqueous carrier (claim 1).

Rasor and Schneider disclose compositions comprising a microparticle and microbubble for methods of ultrasound and/or drug delivery, as discussed above.

Rasor and Schneider fail to disclose that the methods of drug delivery include a step of insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

Unger discloses compositions comprising microbubbles that are useful for both ultrasound imaging and drug delivery, see abstract and column 35, lines 4-5. Unger teaches that the microbubbles may further comprise various drugs that are released by insonation to provide the advantage of site-specific delivery to a desired site, (e.g., the drug is not released until the particles reach the treatment site), (col. 35, lines 29+). Unger also disclosed that the microsphere might be made of starch. This disclosure reads on the requirement of new claim 15 (col. 29, lines 12+), and that the microspheres are preferably sufficiently stable in the vasculature such that they withstand recirculation. The gaseous precursor-filled microspheres may be coated such that uptake by the reticuloendothelial system is minimized. Useful coatings include, for example, polyvinyl alcohol, and starch (col. 19, lines 40+ and).

It would have been obvious to one of ordinary skill in the art to use the compositions disclosed by Rasor or Schneider for drug delivery by insonating the microbubbles at a desired site in vivo because Unger teaches that analogous gas-filled microbubbles may further contain various drugs to yield a drug delivery means having the advantage of site-specific delivery by insonating the microbubbles at a desired site in vivo. One of ordinary skill in the art would have been motivated to employ the drug delivery methods and the materials that form the microspheres disclosed by Unger using the compositions disclosed by Rasor and Schneider to obtain a composition which is useful for both ultrasound imaging and site-specific therapy using a single administration, wherein the insonating step provides release of the drug specifically at the treatment site.

None of the disclosure teaches preparing the composition without a surfactant.

Hugh teaches that there are two general classes of mechanism that can stabilize bubbles. First, slowly permeating gases remain for relatively long times in the bubbles, while other more rapidly permeating gases diffuse in or out according to their concentrations in the environment total pressure inside is greater than that outside because of pressure due to surface tension. Second, structures at the gas-liquid interface can serve as stabilizers; examples are surface-active films (surfactants), surface-active protein that may be denatured, and gelatin (page 2045, right col.). Hugh also discloses that it remains to be seen which stabilizer characteristics give the best signal when bubbles are used for ultrasonic contrast: large elements, many elements, or large compliance. In some circumstances, the ultrasonic signal due to a bubble is proportional to the sixth power of radius, so stabilizing mechanisms that give rise to large bubbles offer far more enhancement of a given signal than mechanisms that make for smaller bubbles (page 2051, left col.).

Accordingly, methods of stabilizing microbubbles other than using surfactants were known in the art at the time the invention was made. It would have been obvious to one of ordinary skill in the art to navigate between the different methods known to use stabilizing mechanisms that leads to more enhancement of the given signal. The expected result would be a microbubble consisting essentially of hydrophobic microparticles that may be formed without a surfactant wherein a microbubble is attached or encapsulate the microparticle.

Response to Arguments

Applicant's arguments filed 5/5/2008 have been fully considered but they are not persuasive. Applicant argues that:

- The as-claimed present invention expressly excludes a surfactant from any composition claimed therein. Thus, the teachings of Rasor or Schneider teach away from the present invention and a skilled artisan, following the teachings of Rasor or Schneider, could not arrive at

the present invention of a composition comprising a microparticle and a microbubble, neither of which comprise a surfactant.

To respond: the as-claimed current invention does not expressly exclude a surfactant from any composition claimed there in since claims 15 and recite compounds that are surfactants or encompass surfactants such as polyvinyl alcohol and cellulose.

- Unger does not teach a composition comprising starch to formulate a microparticle as is taught in the Applicants' invention. Accordingly, Unger alone cannot render the present invention obvious because Unger does not teach the composition of the present invention.

To respond: instant claims do not recite a composition comprising starch. Instant claims are drawn to microbubbles made from at least one of poly(vinyl alcohol), poly(styrene), poly(ethylene), poly(anhydride), poly(ester), starch, cellulose, and ethyl cellulose (claim 15). Or a coating of the microbubble comprising poly(vinyl alcohol), poly(styrene), poly(ethylene), poly(anhydride), poly(ester), starch, cellulose, and ethyl cellulose (claim 16). In addition, Unger is relied upon for teaching insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

- The fabrication, stability, process of loading a microbubble that does not comprise a surfactant with a therapeutic agent, and process of associating a microbubble with a microparticle that also does not compromise a surfactant are not taught by either Rasor, Schneider, or Unger. Because Rasor and Schneider both teach away from the present invention, there would be no motivation to combine Unger with either reference.

To respond: instant microbubbles comprise a surfactant as recited in claims 15 and 16. Thus loading of the microbubble would be the same and there is there is motivation to combine Unger to Rasor and Schneider since both references do not teach away.

- Van Liew is largely a theoretical discussion of the arithmetic relationship between pressures exerted by surface tension, pressure generated by any bubble stabilizer, and the size (i.e. radius) of the bubble in terms of how these terms set the upper and lower limits of bubble size and how bubble stabilization mechanisms behave theoretically.

To respond: All scientific knowledge and advancements started with a theory. however, the factors disclosed by Van Liew (Hugh) are the factors affecting stabilizing the microbubbles that are formed without a surfactant as alleged by instant disclosure.

- Van Liew explicitly states that for different stabilizers, the examples provided are only "crude approximations for real bubbles" (page 2050, column 1, paragraph 2) because as the microbubble experiences changes in pressure, the stabilizer may experience changes in state that affect bubble stability leading to unpredictable alterations of bubble stability depending on changing conditions.

To respond: Van Liew teaches clearly a method of slowly permeating gases remain for relatively long times in the bubbles, while other more rapidly permeating gases diffuse in or out according to their concentrations in the environment total pressure inside is greater than that outside because of pressure due to surface tension (the method does not include a surfactant). Even if it is a crude approximation for real bubbles, the method is disclosed and obviates instant claims.

- Van Liew is a disclosure of methods of stabilizing bubbles and does not provide a clear road map that a skilled artisan could follow to arrive at the present invention either alone or in combination with either Rasor or Schneider.

Van Liew teaches the factors that may affect the stabilization of microbubbles that are made without surfactants. Following the disclosed factors is within the skills of a person of an artisan.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

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